REMARKS

Applicant respectfully requests reconsideration of this application.

Applicant's specification

The Examiner noted an informality in Applicant's specification. The specification has been amended to correct this informality. Specifically, at Example 4, on page 33 of the specification, the spelling of the word, "function" has been corrected.

Accordingly, the objection to the specification may be withdrawn.

35 U.S.C. § 103(a)

Claims 46, 52, and 69-84 were rejected as being unpatentable under 35 U.S.C. § 103(a) over Aqeilan et al. (1999) FEBS Lett. 457(2):271-6, in view of Kim et al. (1997) J. Immunol. 159(4):1666-8, U.S. Patent 6,713,280 (the '280 patent), and Sela and Zisman (1997) FASEB J. 11(6):449-56. Applicant respectfully traverses this ground for rejection and requests reconsideration for at least the following reasons.

Applicant's invention relates to a chimeric, bifunctional molecule that can enter into a cell to induce death of the cell by apoptosis. The chimeric, bifunctional molecule comprises a first functional molecule covalently linked to a second functional molecule. The first functional molecule targets and enters the cell. The second functional molecule targets and induces the death of the cell by apoptosis by regulating the opening of a permeability transition pore complex (PTPC) of mitochondria or a fragment of the PTPC. The chimeric, bifunctional molecule has the formula TARG-TOX. Applicant's invention also relates to the

use of the chimeric bifunctional molecule for inducing cell death by apoptosis and for detecting a cancer cell.

The Office concluded that it would have been obvious to one of ordinary skill in the art at the time of the Applicant's invention to modify the methods taught by the references cited by the Office in order to make a bifunctional, chimeric molecule comprising D-amino acids that enters the cell and induces apoptosis. Office Action, at page 4. According to the Office, "Aqeilan et al. teaches a chimeric protein comprising an apoptosis-inducing protein, namely human Bax protein, for targeted therapy." Office Action at page 3. Yet, the Office does acknowledge that Aqeilan et al. fails to "teach substantially either SEQ. ID. NOs.: 239 or 269," which are among the Bax-derived and HIV-1 tat-derived peptides, respectively, contemplated by Applicant for the TOX and TARG components of the TARG-TOX formula of the claimed invention.

The '280 patent was cited by the Office to show the teaching of intracellular targeting of Bcl-2 by conjugated peptides to inhibit the anti-apoptotic function of Bcl-2. Office Action, pages 3-4. Kim et al. was cited by the Office for its disclosure of the ability of HIV-1 tat to transport tat-conjugated molecules into a cell. Office Action, page 4. The Office also points out that the amino acid sequence, RKKRRQRRR, which is contained within, but by no means, represents SEQ. ID. NO.: 269 of the present application, was also disclosed by Kim, et. al. Finally, Sela & Zisman was cited by the Office to show the teaching that "the inclusion of D amino acids may be an advantage in terms of both specificity and efficacy." Office Action at page 4.

To establish a *prima facie* case of obviousness, three basic criteria must be met. The prior art reference (or references when combined) must teach or suggest all the claim limitations. Also, there must be some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. M.P.E.P. 2142.

All of the Applicant's claims relate to the chimeric bifunctional molecules having the formula: Targ-Tox, as described above, wherein Tox and Targ each consist of a peptide as defined by the claims, and wherein the TARG peptide is covalently linked to the TOX peptide by a peptide linker of 2-18 amino acids. Applicant submits that there was no motivation or suggestion to modify or combine the references to arrive at the claimed invention.

For example, the chimera provided by Aqeilan et al. comprises a full-length Bax protein and a full-length IL-2 protein, neither of which are claimed by the Applicant as components of the Targ-Tox chimera. In Applicant's claims, TARG and TOX are peptide fragments, neither of which are described by Aqeilan et al. Thus, the Aqeilan et al. reference fails to meet the threshold requirement for *prima facie* obviousness. It fails to disclose or support all the claim limitations, such as the covalent linkage of two peptide fragments.

The '280 patent is cited by the Office for its disclosure of "a method of using peptide conjugates for the intracellular targeting of Bcl-2" (Office Action at pages 3-4). The peptide conjugates disclosed by the '280 patent, however, involve the attachment of a non-peptide "carrier group" to an exogenous peptide. Thus, the '280 patent suffers the same deficiencies as the Aqeilan et al. reference. It does not disclose or suggest the covalent linkage of two peptide fragments. Moreover, there is no evidence of record that the '280

patent's non-peptide carrier group is the structural or functional equivalent of Applicant's peptide.

Similarly, but on the other hand, Kim et al. fails to teach the claimed elements of Applicant's invention by not providing any of the claimed peptides relating to the TOX component of the claimed invention, and because the conjugates of this reference involve the attachment of one or more tat peptides to the protein, OVA, via the crosslinker, *m*-maleimidobenzoyl-*N*-hydroxysulfosuccinimide ester, instead of the covalent linkage of two peptide fragments, as contemplated by the Applicants. Therefore, the Kim et al. reference also fails to meet the threshold requirement for *prima facie* obviousness.

In addition, the primary teaching of Kim et al. relates to the entry of OVA into the MHC class I biosynthetic pathway. (See Kim. et al. at page 1667, "Introduction of OVA into the cytosol of cells by conjugation to the *tat* peptide should result in the entry of the protein into the MHC class I biosynthetic pathway.") There is no teaching by Kim et al. of any intracellular fate for a protein transported into a cell by tat peptides, other than entry of the protein into the MHC class I biosynthetic pathway. Kim et al. also clearly fails to establish whether the intracellular fate of a protein transported into a cell by tat peptides is a function of tat or the tat-conjugated protein. Accordingly, it would be impossible for one of ordinary skill in the art to be led by Kim et al. to reach the chimeric, bifunctional molecule, as claimed by Applicants, wherein the second functional molecule targets and induces the death of the cell by apoptosis by regulating opening of a permeability transition pore complex (PTPC) of mitochondria or a fragment of the PTPC.

Last, the additional teachings of Sela and Zisman are directed to uses of D-amino acids. As such, this cited reference does not bear on the chimeric, bifunctional molecule

claimed in the present invention and thus, does not cure the deficiencies of Aqeilan et al., the '280 patent, and Kim et al.

Again, for the above stated reasons, it is improper to combine the teachings of the '280 patent, Kim et al., and Sela & Zisman with the teachings of Aqelian, et al. Applicant courteously emphasizes that none of these secondary references disclose a chimeric bifunctional molecule having the formula: TARG-TOX, as described above, wherein TOX and TARG each consist of a peptide as defined by the claims, and wherein the TARG peptide is covalently linked to the TOX peptide by a peptide linker of 2-18 amino acids. Because the references, even when combined, do not teach or suggest all of the claimed limitations, the threshold requirement for establishing a *prima facie* case of obviousness has not been met. Accordingly, the rejection under 35 U.S.C. §103(a) should be withdrawn.

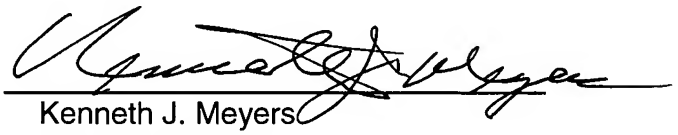
In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 18, 2007

By: 

Kenneth J. Meyers
Reg. No. 25,146
Phone: 202-408-4033
Fax: 202-408-4400
E-mail: Ken.Meyers@Finnegan.com